Treatment Options for Postmenopausal Osteoporosis

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Introduction

Osteoporosis is a process or state of bone loss that results in increased risk for bone fractures. The most important sites of fracture are the spine and hip, although distal forearm and rib fractures are not uncommon.

Sometimes 2 syndromes of osteoporosis are defined: Type I refers to postmenopausal osteoporosis, and Type II is senile osteoporosis.[1] Senile osteoporosis is the gradual process of bone loss that occurs as a result of aging in both women and men. Normally, bone is built up until peak bone mass is attained between the ages of 20 and 35, after which there is a slow progressive loss of bone.[2] Hip fracture is the characteristic consequence of senile osteoporosis.[1]

Postmenopausal osteoporosis is a process that actually begins several years prior to the cessation of menstruation, ie, perimenopausally. The period of most rapid bone loss occurs during the first 5 years after menopause, with continued effects for approximately 3 to 5 years thereafter.[2] Interestingly, men who become hypogonadal during adulthood also go through a period of accelerated bone loss that results in osteoporosis.[3]

The process of postmenopausal osteoporosis probably affects all women to a variable degree. It has been proposed that there are fast losers and slow losers, but this concept has not been established. Bone mineral density can be measured safely and easily to determine a woman's fracture risk.[4] However, relatively high postmenopausal bone density might be a result of high peak bone mass and might not adequately reflect a person's rate of bone loss.

There are several treatment options for postmenopausal osteoporosis: A variety of estrogen preparations, an oral bisphosphonate (etidronate), vitamin D, and calcitonin. Calcium supplements should be a part of any treatment regimen; but in itself is not an adequate treatment.[5-6] Calcium should be supplemented to achieve an intake of 1,500 mg a day; taking it with food improves absorption. It is important to read the label of a calcium supplement carefully to determine its elemental calcium content.

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Estrogen Replacement Therapy

The best-established prevention and treatment for postmenopausal bone loss and fracture is estrogen replacement therapy (ERT)[7] and estrogen is available in many forms.

Historically, the most commonly used is conjugated estrogens (Premarin). The dose of conjugated estrogens usually recommended for ERT is .625 mg daily,[7] which provides full protection against postmenopausal osteoporosis.[8] This is a lower dosage than was commonly prescribed 10 or 20 years ago, but also may be higher than is necessary to treat osteoporosis. There are limited data to suggest that .3 mg of conjugated estrogens combined with 1,500 mg a day of supplemental calcium may produce an equivalent effect.[9] An important reason to prefer the higher dose, however, is its advantage in improving cholesterol metabolism.

Epidemiological data have strongly suggested that ERT is associated with reduced risk for coronary artery disease (CAD).[10-12] Approximately 70% of the women in these studies were using Premarin, which has been shown to lower LDL-cholesterol levels substantially when given in a daily dose of .625 mg; HDL-cholesterol levels are increased slightly. Increasing the dose to 1.25 mg produces little improvement in these results.[13] There appears to be no data indicating that a dosage of .3 mg provides similar benefit. Since lowering LDL-cholesterol levels is known to reduce risk for coronary events, it is very likely that this is one mechanism through which ERT prevents CAD.[13]

The dose response of other forms of estrogen has been studied in an attempt to determine the dosage required to attain full protection against postmenopausal osteoporosis. Piperazine estrone sulfate (Ogen) will provide full protection when given in a dose of 1.25 mg daily. A dosage of .625 mg also provides substantial benefit and was originally thought to be fully adequate,[14] but longer term studies demonstrated that the higher dosage was necessary.[15] The dose-response relationship between this form of ERT and lowering of LDL-cholesterol levels has not been studied.

Transdermal estradiol (Estraderm) is available for the prevention of osteoporosis and is available in 2 doses: 50 mcg and 100 mcg. Here again, the lower dose provides some protection, whereas the higher dose is fully adequate.[16] Transdermal estroadiol has little effect on lipoprotein metabolism,[13] which is an obvious disadvantage, in general. Occasionally, transdermal estradiol may provide an advantage to women with

hypertriglyceridemia, in whom oral estrogen use may exacerbate this problem. Transdermal estradiol, unlike some oral estrogens, also does not raise levels of various liver proteins such as renin substrate.[17]

Oral micronized estradiol (Estrace) is available for ERT. Two mg of oral estradiol is equivalent to .625 mg of conjugated estrogens in its effect to lower LDL-cholesterol levels.[13] Oral estradiol in a daily dose of .5 mg to 2.0 mg provides protection against postmenopausal osteoporosis, but it is unclear which dosage is the minimum required to provide full protection.[18]

There are other estrogen preparations that are being marketed for ERT; for example, esterified estrogens. Little is known about appropriate dosing of esterified estrogens, although they are being used as a substitute for conjugated estrogens. These 2 products are not equivalent in terms of their USP formulations: Conjugated estrogens have 35% equine estrogens; esterified estrogens have 10%.[19]

Treatment Alternatives

Why consider alternatives to ERT? There are several reasons. Estrogens are believed to be contraindicated in patients with a history of breast or endometrial cancer, and in patients with a history of thrombo-embolic disease.[20] Oral estrogens probably should not be given to women who are at risk for severe hypertriglyceridemia.

Postmenopausal estrogen use can result in menstrual bleeding. When medroxyprogesterone acetate (Provera) is used together with estrogens in a cyclical fashion (eg, 10 mg on days 15 to 25 of the cycle) monthly withdrawal bleeding is to be expected. When lower doses of this progestagen (eg, 2.5 mg to 5.0 mg) are used concurrently with the estrogen throughout the month, bleeding is less frequent.

Concurrent estrogen and progestagen use results in unwanted menstrual bleeding more often in women who begin ERT shortly after menopause than in women who are older. Sometimes, a lower dose of the estrogen and/or a higher dose of the progestagen may eliminate this problem. Nevertheless, for some women, menstrual bleeding remains an unacceptable side-effect of ERT.

Some women develop breast tenderness when they start taking estrogens after menopause. This occurs more often at higher doses, but can occur in some women at relatively low doses. These women frequently discontinue ERT because of the discomfort.

Some women fear the development of breast cancer as a consequence of ERT. Currently, the relationship between ERT and the risk of breast cancer is somewhat controversial. One meta-analysis arrived at a relative risk of 1.3 in association with ERT.[21] It is unlikely that this meta-analysis underestimates the risk. Although the use of a progestagen eliminates the increased risk of endometrial cancer resulting from the use of estrogen alone,[22] the notion that the progestagen also attenuates the risk for breast cancer is without foundation.

In responding to a patient's fear of ERT causing breast cancer, the physician is advised to try to determine whether this fear is deeply rooted and unshakeable or is open to influence. The epidemiological data strongly suggests that women who use ERT live longer than those who do not, with reduced risk for CAD.[12,23] But not every patient is equally impressed. In particular, ERT may not be acceptable to a woman whose mother or sister had breast cancer.

The alternatives to ERT include etidronate, vitamin D, and calcitonin. Among the 3, use of etidronate[24-25] and vitamin D[26] have been shown to prevent loss of bone mineral density and occurence of fracture, whereas salmon calcitonin use has been associated with prevention of bone mineral density loss only.[27]

Etidronate (Didronel) is given in a dose of 400 mg a day for 2 weeks out of every 3 months.[24-25] Calcium, magnesium, and a variety of foods interfere with its absorption, so it is best taken on an empty stomach at bedtime. The response to etidronate (and other alternative treatments) should be monitored after a year of therapy to be assured it is working. Ineffective treatment could be related to inadequate absorption.

Vitamin D is another treatment that can be given orally. Although its efficacy is controversial, at least 1 study has demonstrated that calcitriol (Rocaltrol) taken in a dosage of .5 mcg daily preserves bone mineral density and prevents fractures.[26] The risks of calcitriol are related to the possible developments of hypercalcemia and/or hypercalciuria. Therapy should be monitored and the dosage of calcitriol reduced if serum calcium exceeds the upper limit of normal or if 24-hour urinary calcium is excessive, ie, >250 mg to 300 mg.

Calcitonin must be given parenterally and the initial dose should be low. Flushing and nausea commonly occur in the beginning, but often diminish or disappear with continued therapy. The dosage should be gradually increased to 100 IU of salmon calcitonin (Calcimar, Miacalcin) a day.[27] Human calcitonin also is available, but the equivalency of dosing is uncertain, the cost is higher, and it has no apparent clinical advantage.

The best-established prevention and treatment for postmenopausal osteoporosis is estrogen replacement therapy. Premarin has the advantage of being the estrogen most closely associated with the coronary-protective effects observed in epidemiological studies and has a beneficial effect on the lipid profile in most women. However, other estrogen preparations, when used at appropriate dosages, provide equal protection against osteoporosis and also can be cardioprotective. For women who should not or wish not to use estrogen, currently available alternative treatments for osteoporosis include etidronate, vitamin D, and calcitonin. Calcium supplementation to maintain a total intake of 1,500 mg a day also is generally advised.

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Postpartum Preeclampsia Complicated by Acute Pulmonary Edema

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ing therapy with the agent, although reported cases of pulmonary edema up to 72 hours after discontinuation of therapy have been reported. Our patient developed pulmonary edema almost 3 weeks after discontinuation of oral terbutaline, and it is unlikely that tocolytic therapy played a significant role in her presentation.

Peripartum cardiomyopathy is another possible etiology in patients presenting with postpartum pulmonary edema. These patients typically present within 4 weeks antepartum and 5 months postpartum.[6] Alternatively, the contribution of this patient's previous treatment of Hodgkin's disease with chemotherapy and radiation therapy in her presentation is unclear. Both chemotherapeutic agents and mediastinal radiation therapy can cause myocardial toxicity leading to left ventricular dysfunction.[7-8] Our patient, however, had no evidence of left ventricular dilation or systolic dysfunction on echocardiogram to suggest either peripartum cardiomyopathy or cardiomyopathy secondary to chemotherapy or radiation therapy.

In summary, postpartum acute pulmonary edema is a rare but well-described complication of pregnancy. Multiple possible etiologies including peripartum cardiomyopathy, pulmonary edema associated with tocolytic therapy, and pulmonary edema secondary to preeclampsia-eclampsia need to be considered in these patients. In previous reports of patients with pulmonary edema associated with preeclampsia, all patients had antepartum evidence of preeclampsia. In this case report, we describe a case of early postpartum pulmonary edema in a patient with postpartum preeclampsia following a relatively normal gestation and delivery.

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